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"ALPHA PARICLE EMITTERS IN MEDICINE"

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MASTER

ALPHA-PARTICLE EMITTERS IN MEDICINE

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ABSTRACT

Radiation-induced cancer of bone, liver, and lung has been a prominent harmful side-effect of medical applications of alpha emitters. In recent years, however, the potential use of antibodies labeled with alpha emitting radionuclides against cancer has seemed promising because alpha particles are highly effective in cell killing. High dose rates at high LET, effectiveness under hypoxic conditions, and minimal expectancy of repair are additional advantages of alpha emitters over antibodies labeled with beta emitting radionuclides for cancer therapy. Cyclotron-produced astatine-211 (^{211}At) and natural bismuth-212 (^{212}Bi) have been proposed and are under extensive study in the United States and Europe. Radium-223 (^{223}Ra) also has favorable properties as a potential alpha emitting label, including a short-lived daughter chain with four alpha emissions. The radiation dosimetry of internal alpha emitters is complex due to nonuniformly distributed sources, short particle tracks, and high relative specific ionization. The variations in dose at the cellular level may be extreme. Alpha-particle radiation dosimetry, therefore, must involve analysis of statistical energy deposition probabilities for cellular level targets. It must also account fully for nonuniform distributions of sources in tissues, source-target geometries, and particle-track physics.

INTRODUCTION

Alpha particles are energetic, positively charged helium nuclei emitted from the nuclei of heavy elements because the binding energy

per nucleon (or packing fraction) has fallen below a critical value. Alpha-particle decay is typical of many of the heaviest known radionuclides, both natural and man-made. For example, natural thorium-228 decays by alpha emission to radium-224, and cyclotron-produced astatine-211 decays by alpha emission to bismuth-207. Most alpha emitters in the environment are members of the natural uranium-238 and thorium-232 decay series. Others, such as plutonium-238, are produced during nuclear reactions. The physical half-lives of alpha emitters are constants ranging from milliseconds to billions of years, depending on the radionuclide.

The energy released to matter by alpha particles emitted from atomic nuclei is distributed along very short (30-70 μm in tissues), straight tracks having a high ionization density. This distribution is very different from tracks produced by beta particles and gamma rays. The characteristics of energy deposition by alpha particles in matter are important in assessing their potential to produce biological damage. The radiation dosimetry for alpha emitters must address energy distribution on a microscopic scale to account for the probability of irradiating single cells. A cellular level approach to alpha-particle dosimetry is key to understanding why alpha particles are considerably more effective per unit energy imparted in producing radiobiological effects than beta or gamma radiation.

This paper covers fundamental concepts of alpha-particle dosimetry and microdosimetry and the radiobiological significance of alpha-particle energy deposition in small sites. It also briefly reviews the historical applications of alpha emitters in medicine and the potential for new applications in the treatment of disease.

HISTORICAL PERSPECTIVE

Shortly after natural radioactivity was discovered in 1896 by Becquerel, Soddy and Rutherford showed that naturally radioactive substances were mixtures of several isotopes. They separated radium-224 (^{224}Ra) from thorium in 1902. This radionuclide with its abundant

alpha emissions was used in dermatology for skin lesions and for treatment of rheumatic diseases (1). Radium-224 was first used in 1912 for treatment of ankylosing spondylitis (with limited success) and later for tuberculosis (not effective).

Bottled radium solutions as the stimulant, "Radithor" were prescribed to cure almost any ailment. Radium appeared to ease the pain associated with inflammation, stiffening, and crookedness of the vertebral column in ankylosing spondylitis patients and to ease the movement of joints in the treatment of rheumatoid synovitis.

Death resulted from acute radiation syndrome in early patients administered large oral doses of ^{226}Ra solution, and internal applications were discontinued for a period of time. The intravenous injection of ^{224}Ra against rheumatic disease began again in France in 1922, in England in 1946, and in Germany in 1947. The use of ^{224}Ra in treatment of ankylosing spondylitis resumed in 1964 in France. Favorable results encouraged further use of ^{224}Ra against rheumatoid arthritis (2). Radium-224 is still used for treating adult spondylitic patients in Germany, but current doses are considerably smaller than those given earlier.

The major late effects of ^{224}Ra have been bone cancers induced by the bone-surface-seeking radium and radioactive daughter products. A long-term follow-up of ^{226}Ra watch dial painters also showed malignant bone tumors and carcinomas of the mastoids and paranasal sinuses.

Thorium colloid (Thorotrast) containing thorium-232 and decay-series daughter products was given as a contrast medium for radiographic examinations (such as cerebral angiography), primarily in Germany, starting as early as about 1920 and continuing until recently. Liver tumors and leukemia have been the most significant late side-effects of Thorotrast (3). Recent network television documentaries have described liver cancer incidence among several contemporary American Thorotrast patients.

POTENTIAL APPLICATIONS AGAINST CANCER

Ironically, alpha emitters now promise to be highly effective against cancer when administered as immunoconjugates (4-8). Among the advantages of alpha emitting radionuclides over other possible choices are:

1. higher dose rates with high linear energy transfer (LET), and therefore
2. more efficient cell killing
3. nonreparable cellular damage
4. effectiveness under hypoxic conditions
5. more selective irradiation of tumor cells and sparing of normal tissues.

The last advantage has been described by Humm, Chin, and Cobb (9) as a "geometric enhancement factor" favoring the inactivation of cells by alpha emitters when compared to beta emitters.

Some of the disadvantages of alpha emitters have been discussed in the literature. Many alpha emitters have short half-lives, limiting their application in medicine, and are expensive to produce. As labeled immunoconjugates, their high dose rates in solution can lead to extensive physical damage of the protein and a decrease of immunospecificity during preparation or before cancer cells are targeted. Radiation safety aspects of handling alpha emitters may also be somewhat more complicated than for pure beta and beta-gamma emitters. The limited range of alpha particles could make them ineffective in the treatment of some solid tumors if tumor cell labeling is not uniform.

Alpha emitting immunoconjugates of potential medical application have been successfully used to cure ascites after intraperitoneal

injection in mice (7,8), to selectively ablate B-cell lymphocytes in mice (5), and to increase the median survival time of mice with T-cell lymphoma (4). Human trials are expected in the near future.

Most alpha emitters are isotopes of elements that are taken up by bone during growth and remodeling. Short-lived alpha emitters on bone surfaces could lead to induction of bone cancer. However, bone cancer should not be of concern as a secondary toxicological late effect of an alpha labeled immunoconjugate for the following reason: a tightly conjugated alpha emitter should express the biological retention, distribution, and clearance of the host protein rather than that of a free, bone-seeking radionuclide. Immunoconjugates targeting cancer cells should effectively deliver the alpha emitter to those cells, whereas immunoconjugates not finding tumor cells should be rapidly excreted from the body. The immunoconjugate would not be taken up by bone. Radioactive daughter products, however, may break away from the protein during transformation and recoil, and may therefore behave as free ions in biological media.

CHARACTERISTICS OF ALPHA-PARTICLE TRACKS

Alpha particles emitted from the atomic nuclei of unstable radionuclides have an exit energy of 1.8 to 11.6 MeV, depending on the radionuclide. Energies, half-lives and yields of some important alpha emitters are given in Table 1. Some alpha emitters exhibit "branching decay." For example, bismuth-212 decays 34% of the time by alpha emission and 66% of the time by beta emission. The beta-decay daughter product polonium-212 then decays by alpha emission to stable lead-208. Thus, there are effectively one 6.07 MeV alpha particle and two 8.78 MeV alpha particles from every three decays of bismuth-212.

Alpha particles are helium nuclei ejected from the nuclei of unstable heavy elements with initial kinetic energies typically in the range of about 4 to 8 MeV (Table 1). As heliuim nuclei, they carry a positive charge of 2 and interact strongly with atomic electrons as

TABLE 1. ENERGY, HALF-LIFE, YIELD,* AND DAUGHTER PRODUCT OF SOME COMMON ALPHA EMITTERS

Radionuclide Product	Mean α Energy (MeV)	Physical Half-Life	Yield* (%)	Daughter
Thorium-232	3.98	14.1 billion y	100	radium-228
Uranium-238	4.17	4.51 billion y	100	thorium-234
Radium-226**	4.78	1,600 y	100	radon-222
Plutonium-239	5.14	24,400 y	100	uranium-235
Polonium-210	5.30	138 d	100	lead (stable)
Americium-241	5.47	458 d	100	neptunium-237
Plutonium-238**	5.48	86 y	100	uranium-234
Radium-224**	5.67	3.64 d	100	radon-220
Radium-223**	5.67	11.43 d	100	radon-219
Actinium-225	5.79	10.0 d	100	francium-221
Astatine-211	5.87	7.21 h	42	bismuth-207
branching decay, electron capture			58	polonium-211
→polonium-211	7.45	0.5 s	99	lead (stable)
Bismuth-212**	6.07	60.6 m	34	thallium-208
branching decay, beta			66	polonium-212
→polonium-212	8.78	0.3 μs	100	lead (stable)

* Yield = percentage of all decays resulting in alpha emission.

** Applications in medicine: Radium-226 for brachytherapy sources, plutonium-238 for battery packs (artificial hearts), radium-223 for immunoconjugates (also astatine-211, actinium-225, and bismuth-212).

they pass through matter, producing ionizations and excitations and giving up energy in the process. On average, about 34 eV are

expended for each ion pair produced; thus, many atoms or molecules are ionized during the interaction of alpha particles with matter. The particle "track" is a pattern of dense ionization events that can be directly associated with eventual subcellular biological damage.

A portion of a 6 MeV alpha-particle track is shown in Figure 1. The x's represent primary ionizations, and the solid dots represent secondary ionizations from electrons (delta rays) that have been energized by the alpha particle. Alpha particles follow straight paths, whereas secondary electrons radiating from the dense central core of the track follow a somewhat random path in the forward direction. The effective radius of the track is about 60 nm (0.06 μm). The range of the particle is a function of energy and stopping material. An empirical formula for estimating the range of alpha particles in soft tissue was derived by Polig (10) from experimental data:

$$R_o = 3.62\ E^{1.43} \qquad (1)$$

where R_o is the alpha particle range in micrometers (μm), and E is its initial kinetic energy in MeV.

The approximate alpha-particle range in tissue relative to the range in air may be derived from the Bragg-Kleeman rule (11):

$$R_m/R_{air} = (\rho_{air}/\rho_m)(A_m/A_{air}) \qquad (2)$$

where R_m is the range of the alpha particle in tissue, R_{air} is the range in air, ρ is the density of air or tissue, and A is the effective atomic weight of tissue or air. The effective atomic weight of an absorbing medium is determined from the relationship:

$$(A_{eff})^{-1/2} = f_1/(A_1)^{1/2} + f_2/(A_2)^{1/2} + \ldots, \qquad (3)$$

where f_1 is the fraction by weight of atom 1, A_1 is the atomic weight of atom 1, etcetera, for the different atoms comprising each substance.

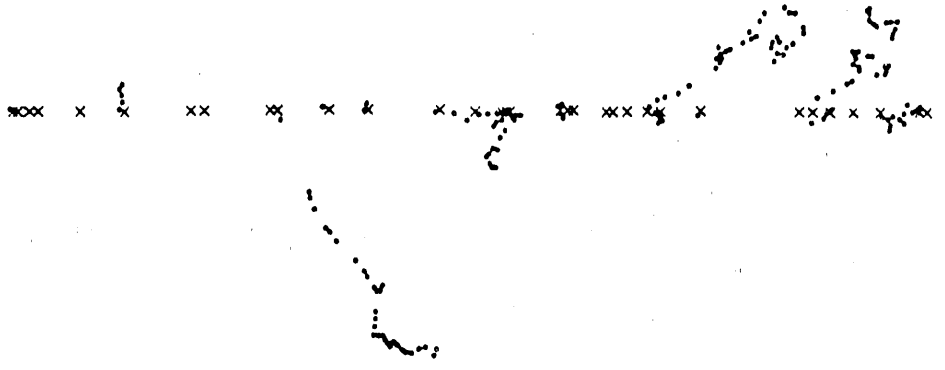

FIGURE 1. Computer-generated segment of hypothetical charged-particle track. Crosses represent primary ionizations along central core of track, and dots represent secondary ionizations forming delta-ray secondaries.

The relative specific ionization (dE/dx) per unit track length increases according to the familiar Bragg curve (Fig. 2), and more energy is expended near the end of the alpha particle track than at the beginning. The value dE/dx may increase by a factor of 2.5 to 3.0 near the end of the track. The mean linear energy transfer (LET) is the mean energy imparted per unit track length. LET, also known as collision stopping power, can be defined in terms of dE/dx, where dE is the mean energy lost by a charged particle along a distance dx of its trajectory. For example, a 5.5 MeV particle traveling 38 μm in soft tissue would have an LET of 5,500 keV/38 μm = 145 keV/μm. Alpha particles have high LET, whereas beta particles have low LET. In general, the LET increases with particle charge and decreases with particle velocity.

"TARGET" SITES

Alpha particles impart energy to all matter along the path. The "target" is the biologically important solid volume of mass m intersected by the particle. It could be the whole organ (lung, liver,

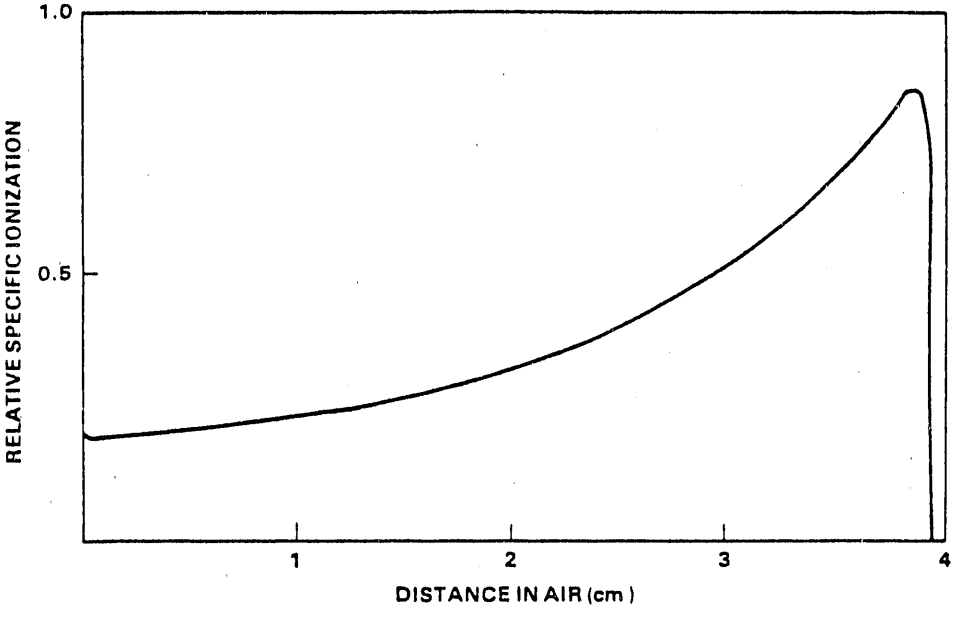

FIGURE 2. Bragg curve for alpha particles.

kidney, etc.), tumor or micrometastasis, clump of cells or a single cell, or any solid volume considered for purposes of radiation dosimetry. It could also be the nucleus of a cell or a smaller volume within the nucleus. In other words, the target is defined by the user; it is the biological structure for which effects of alpha particle radiation are evaluated.

The effects of radiation begin at the subcellular level. Radiation damage to tissues is considered significant if certain functional capabilities or the viability of cells is affected. A wide variety of cytopathologic changes is possible in irradiated cells. Alpha particles that intersect the cytoplasm without imparting energy to the nucleus are usually not considered to be harmful to cell function and viability.

However, cell death is likely if an alpha particle "hits" the nucleus, and thus the nucleus is an excellent choice of a "target" for radiation dose calculations. Diameters of cell nuclei in the body range from about 3 to 15 μm, depending on the cell type, the phase within the cell cycle, and cell division. For some, the critical biological target is a 1-μm or smaller sphere within the nucleus containing the location of double-strand DNA breaks after irradiation.

The exact mechanisms of radiation damage leading to different kinds of cellular and subcellular effects are still being studied to determine the relationship between the amount of energy imparted and the probability of those effects. For a given target, the radiation dose may be determined if the distribution and number of alpha emitting sources are known.

ABSORBED DOSE CALCULATIONS

The basic quantity describing the energy imparted to matter is the absorbed dose. The absorbed or "average" dose is the mean value of many energy deposition events in small targets. By definition, the absorbed dose D is the quotient of $d\bar{\varepsilon}$ by $d\bar{m}$, where $d\bar{\varepsilon}$ is the mean energy imparted by ionizing radiation to matter of mass $d\bar{m}$ (12):

$$D = d\bar{\varepsilon} / d\bar{m}. \quad (4)$$

[The special name for the unit of absorbed dose is the gray (1 Gy = 1 J/kg), although many dosimetrists still prefer to use the term rad (1 rad = 0.01 J/kg)].

The absorbed dose rate (Gy/day) within a large, uniform volume source is

$$D = CBE/m, \quad (5)$$

where C is an energy conversion constant (0.512 g Gy/MeV μCi day), B is the activity of the alpha emitter (μCi) in a volume of m (g), and

E is the average energy (MeV) per disintegration. It therefore follows that the absorbed dose (Gy) from an internal emitter with a known biological retention is

$$D = (0.512\ E\ f\ A_o\ /m) \int_0^t B(t)dt \qquad (6)$$

where f is the fractional yield of alpha particles per radioactive decay, A_o is the initial activity (μCi), and B is the effective retention over time t. For a single exponential clearance and a known fraction remaining at time t, the absorbed dose is

$$D = (-0.512\ E\ f\ A_o\ t/m)[(1-F)/(\ln F)]\ . \qquad (7)$$

where F is the fraction of A_o remaining at time t.

The approximate "average" dose to a microscopic target for a single "random" traversal may be calculated as follows: Given a 5.5 MeV alpha emitter, a target diameter of 8 μm, and a mean chord length of (2/3)*diameter = 5.33 μm,

$$D(Gy) = \bar{e}/m, \qquad (8)$$

where $\bar{e}$ = (5.33/38)(5.5 MeV) [the energy imparted over the chord],

= 0.77 MeV, or 1.23×10^{-6} erg, and

where m = $d^3/6\pi$ g/cm^3 [mass = volume * density]

= 2.68×10^{-10} g. Therefore,

$$D(Gy) = 1.23 \times 10^{-6}\ erg/(2.68 \times 10^{-10}\ g)(100\ rad/Gy)$$

$$= 0.461\ Gy.$$

The actual dose to the target will depend on the exact chord length taken by the alpha particle and the actual amount of energy deposited. The number of alpha particle "hits" and their traversal chord length

will usually depend on the geometrical relationship between the spatial distribution of alpha emitting sources and the spatial distribution of targets.

Conventional dose-averaging neglects the stochastic variations in dose at the microscopic level due to track-structure detail, target size, chord length through the target, and relative specific ionization with distance traveled. Microdosimetry, however, takes these into account.

MICRODOSIMETRY CALCULATIONS

Concepts of internal microdosimetry were developed by Roesch (13) from the theory and quantitative formulations of Rossi (14,15), Kellerer (16), and others. Simply stated, microdosimetry is a statistical analysis of the probability of small targets receiving any possible radiation dose.

Since each target (for example, a cell nucleus) receives a unique dose depending on the exact chord length for each alpha particle "hit," the number of hits, and the total amount of energy deposited, a probability histogram may be constructed indicating the relative frequency of any such dose.

The exact amount of energy imparted to a microscopic target is the specific energy (z). It is defined as the quotient of e by m, where e is the energy imparted by ionizing radiation to a small target having mass m:

$$\bar{z} = e/m \tag{9}$$

The specific energy may be due to one or more energy-deposition events. The possible values of the specific energy are described by a probability density, f(z). The mean specific energy is the absorbed dose, D, and has the same units as the absorbed dose:

$$\bar{z} = D \tag{10}$$

The probability density also includes the probability that no energy is deposited in a site, or z = 0. This component, called the delta function (δ), is the fraction of unirradiated sites.

$$\delta = \exp(-M), \text{ or} \tag{11}$$

$$M = -\ln \delta , \tag{12}$$

where M is the mean number of "hits" per target. The delta function can be a useful parameter for interpreting microdosimetry distributions for radiobiological experiments.

The lineal energy, or event size (y) is the quotient of e by $\bar{T}$, where e is the energy imparted to matter in a microscopic volume of interest by an alpha particle interaction, and $\bar{T}$ is the mean chord length in that volume resulting from random straight-line traversals of the volume:

$$y = e/\bar{T} \tag{13}$$

If that volume is a sphere with diameter d, then the mean chord length is

$$\bar{T} = 2d/3, \text{ and} \tag{14}$$

$$y = 3e/2d. \tag{15}$$

Lineal energy is a stochastic quantity subject to a geometric cut-off rather than an energy cut-off. For spherical targets, lineal energy and specific energy due to a single energy deposition event are related by the equation

$$z = (4/\rho S)y \tag{16}$$

where ρ is the density of matter in the volume, and S is the surface area of the target. The mean lineal energy is similar in concept to the LET and has the same dimensions and units.

The concepts of specific energy and lineal energy form the foundation of stochastic microdosimetry. Microdosimetry involves the calculation or experimental determination of probability densities in specific energy for various types of radiation and various sizes of the target. The probability density corresponds to the distribution of doses actually received by cells or cell nuclei in a biological system and includes the probability that such targets are not irradiated. The calculations are complex and must be performed using computer techniques.

CALCULATION OF SPECIFIC ENERGY DISTRIBUTIONS

Probability densities in specific energy may be calculated using the mathematical methods of Roesch (13). The spatial distribution of alpha emitting sources is first defined. The probability density is calculated for a point source at any distance from a cell nucleus or other specified target. The probability is then determined from the spatial distribution of sources that a point source exists at any given distance from the target. The densities from all point sources are then convoluted using Fourier transforms to construct a new specific energy density for the target population. All possible angles of intersection and the relative specific ionization per unit length must be taken into account. The low-energy contributions of delta-ray electrons must also be accounted for.

An example of a probability density in specific energy is shown in Figure 3. This figure is a histogram of doses to cells exposed to a certain activity concentration of the alpha emitter americium-241 in culture medium for about 5 hours, where the average dose is about 0.7 Gy and 22% of the targets receive no dose (the delta function). The shape of the curve and the relative values of the dose distribution give information about the probable effectiveness of the irradiation to produce biological effects. Many aspects of the relationship between the probability density in specific energy and associated biological effects remain to be determined.

Point-kernel methods for evaluating the "radiation field" around an

alpha emitting source incorrectly assume that the ionization field within alpha particle range of the source is uniform at each distance for which the absorbed dose is estimated. Such methods do not provide probability densities in specific energy, delta functions, or hit probability and should not be used for evaluating the biological effectiveness of alpha emitters on microscopic targets.

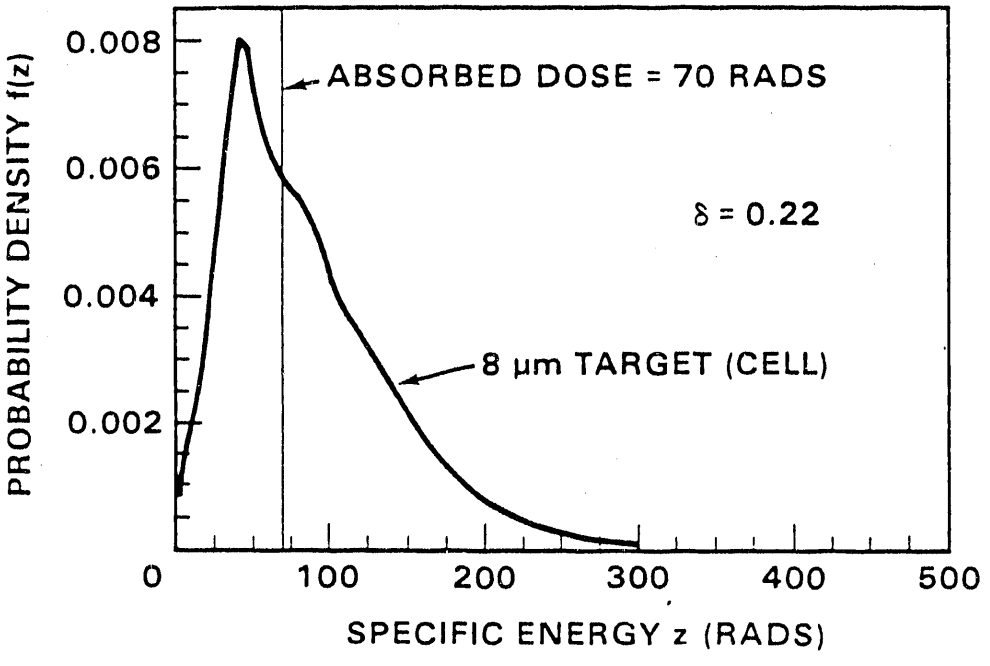

FIGURE 3. End-product of a microdosimetry calculation: example of probability density in specific energy for uniformly distributed americium-241 source in unit-density medium containing 8-μm-diameter targets. Delta function (δ) is fraction of sites with no energy deposition.

WHEN IS MICRODOSIMETRY TO BE APPLIED?

Microdosimetry is a statistical analysis of the relative frequency of doses to small targets in a biological system. The variation in dose

from one target to another becomes smaller with increasing target diameter and increasing absorbed dose. The variation increases with smaller targets and lower absorbed doses. If the mean deviation of the specific energy from the absorbed dose exceeds about 0.2, then the stochastic variability of the dose should be considered. Microdosimetry should generally be applied for studies evaluating radiobiological effects on targets having diameters less than 100 μm and for absorbed doses less than 10 Gy.

RELEVANCE OF ALPHA-PARTICLE DOSIMETRY TO RADIOIMMUNOTHERAPY

The objective of radioimmunotherapy is to employ an antibody specifically directed against selected tumor-associated antigens of malignant cells, couple a radionuclide to the antibody, and administer the complex to a cancer patient. If the immunoconjugate binds to the membrane of a cancer cell, the probability is good that the radiation emitted will hit the cell nucleus. Multiple antibody/radionuclide conjugates per targeted tumor cell should be sufficient for complete cell killing and destruction of tumors or metastases. Reduced concentrations of radiolabeled antibody in normal tissues allow for tissue sparing.

Alpha emitters should be particularly effective in cell killing and sparing of normal tissues due to their short range and high LET. Alpha emitters previously considered for radioimmunotherapy include astatine-211, bismuth-212, actinium-225 and radium-223. Actinium-225 and radium-223 each emit four alpha particles by their decay and the decay of short-lived daughter products, greatly increasing their potential antitumor effectiveness per unit activity administered. Microdosimetric evaluations of the potential for alpha emitters in radioimmunotherapy have been performed for bismuth-212 (17) and for astatine-211 (9).

The absorbed dose to a tumor containing an alpha emitting immunoconjugate is an important parameter for comparing the relative

effectiveness of different levels or concentrations of activity over time. In practice it will not be possible to determine the probability density in specific energy to a tumor or normal tissue unless tissue specimens are examined autoradiographically and many complex calculations are performed. Microdosimetry calculations can be particularly valuable, however, for unraveling the complicated dose-response relationships in carefully controlled irradiations of mammalian cells in vitro. Microdosimetry is a tool for interpreting the radiobiology and not for routine clinical dosimetry calculations.

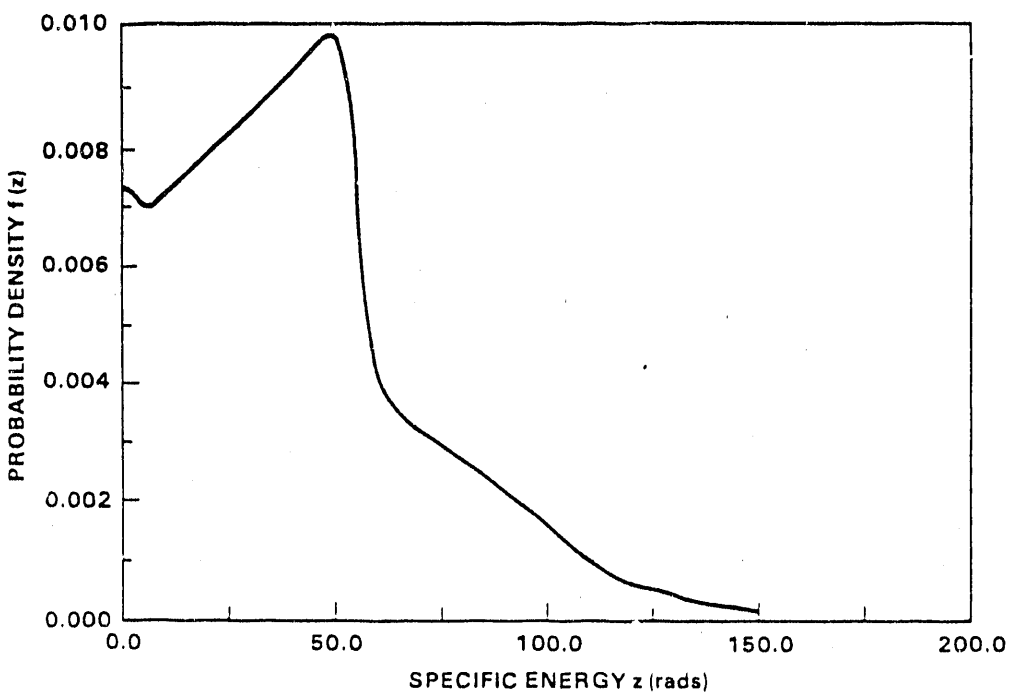

FIGURE 4. Probability density in specific energy for alpha particle emitted from surface of cell membrane. Prevalence of low-energy contributions to cell dose is shown.

Because radioimmunoconjugates bind to antigen sites on cell membranes, the probability density in specific energy will shift to the left, meaning that the relative number of biological targets (or cell nuclei) receiving lower radiation doses will increase. This effect is shown in Figure 4. When the alpha particle originates from the cell membrane, there is both an increased probability of an energy deposition event in the cell nucleus and increased probability that the total dose to the target will be less than in the case where the sources are uniformly distributed in the medium (compare the shape of the curve to the one in Fig. 3). High doses mean that much energy is wasted in "over-kill" and that the effect is not necessarily increased with increasing dose. Alpha labeled immunoconjugates should therefore be highly effective as antitumor agents because the alpha energy is more judiciously utilized, and the probability of hitting the nucleus with sufficient energy to kill the cell may be optimized with greater sparing of normal tissue.

SUMMARY

Alpha emitters have current applications in medicine, particularly in radioimmunotherapy. To be effectively used, however, the radiation dosimetry must be well characterized at the cellular level. This characterization requires analysis of the probability density in specific energy imparted to microscopic targets of biological importance to both cell killing and other nonlethal endpoints. The critical target for microdosimetry calculations and internal alpha emitters should be the cell nucleus. The spatial distributions of both the alpha emitting sources and the target cell nuclei must be determined to calculate probability densities in specific energy. The shape of the probability density curve relates to the biological effectiveness of the irradiation. The absorbed (average) dose is an important parameter that may be correlated with biological effectiveness as long as the spatial distributions of alpha sources and biological targets remain constant (18). When these spatial distributions change, however, the biological effectiveness of the alpha emitter may also be expected to vary. Other important parameters for evaluating the effectiveness of internal alpha

emitters are the delta function (fraction of biological targets completely missed) and the probabilities of 1, 2, 3 ... n number of hits.

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REFERENCES

1. Shales F. Brief history of Ra-224 usage in radiotherapy and radiobiology. Health Phys 1978; 35:25-32.

2. Bertrand B, Legras A, Martin J. Use of radium-224 in the treatment of ankylosing spondylitis and rheumatoid synovitis. Health Phys 1978; 35:57-60.

3. Van Kaick G, Lorenz D, Muth H, Kaul A. Malignancies in German Thorotrast patients and estimated tissue dose. Health Phys 1978; 35:127-136.

4. Harrison A, Royle L. Efficacy of astatine-211-labeled monoclonal antibody in treatment of murine T-cell lymphoma. National Cancer Institute Monographs 1987; 3:157-158.

5. Black CV, Atcher RW, Barbet J, Brechbiel MW, Holton OD, Hines JJ, Gansow OW, Weinstein JN. Selective ablation of B lymphocytes in vivo by an alpha emitter, bismuth-212, chelated to a monoclonal antibody. Immunoconjugates and Radiopharmaceuticals 1988; 1:43-53.

6. Kurtzman SH, Russo A, Mitchell JB, DeGraff W, Sindelar WF, Brechbiel MW, Gansow OA, Friedman AM, Hines JJ,

Gamson J, Atcher RW. Bismuth-212 linked to an anti-pancreatic carcinoma antibody: Model for alpha-particle-emitter radioimmunotherapy. J Natl Cancer Inst 1988; 80:449-452.

7. Macklis RM, Kaplan WD, Ferrara JL, Atcher RW, Hines JJ, Burakoff SJ, Coleman CN. Resident's essay award: Alpha particle radioimmunotherapy: Animal models and clinical prospects. Int J Radiat Oncol Biol Phys 1989; 16:1377-1387.

8. Macklis RM, Kinsey BM, Kassis AI, Ferrara JL, Atcher RW, Hines JJ, Coleman CN, Adelstein SJ, Burakoff SJ. Radioimmunotherapy with alpha-particle-emitting immunoconjugates. Science 1988; 240:1024-1026.

9. Humm JL, Chin LM, Cobb L. Microdosimetry in radioimmunotherapy. In: Proceedings Tenth Symposium on Microdosimetry, Rome, Italy, May 21-25, 1989. Radiat Prot Dosim. In press.

10. Polig E. The localized dosimetry in internally deposited alpha-emitters. In: Ebert M, Howard A, eds. Current Topics in Radiation Research, Vol. 13. Amsterdam: North-Holland Publishing Company; 1978:189-327.

11. Mays CW. Determination of localized alpha dose I, Radiobiology Laboratory, College of Medicine, University of Utah, Semi-Annual Progress Report C00-217, 1958. Salt Lake City, Utah: University of Utah; 1958:161.

12. International Commission on Radiation Units and Measurements, Radiation Quantities and Units, ICRU Report 33. Bethesda, MD: International Commission on Radiation Units and Measurements; 1980.

13. Roesch WC. Internal microdosimetry. Radiat Res 1977; 70:494-510.

14. Rossi HH. Energy distribution in the absorption of radiation. In: Advances in Biological and Medical Physics, Vol. 11. London: Academic Press; 1966:27.

15. Rossi HH. Microscopic energy distribution in irradiated matter. In: Attix FH, Roesch WC, eds. Radiation Dosimetry, Vol. I. New York: Academic Press; 1968:43-92.

16. Kellerer AM. Analysis of patterns of energy deposition: A survey of theoretical relations in microdosimetry. In: Ebert HB, ed. Proceedings Second Symposium on Microdosimetry. Brussels: Commission of the European Communities; 1970:107-134.

17. Fisher DR. The microdosimetry of monoclonal antibodies labeled with alpha emitters. In: Schlafke-Stelson AT, Watson EE, eds. Fourth International Radiopharmaceutical Dosimetry Symposium, 1985, CONF-85113. Oak Ridge, TN: Oak Ridge Associated Universities; 1985:26-36.

18. Fisher DR, Frazier ME, Andrews TK0 Jr. Energy distribution and the relative biological effects of internal alpha emitters. Radiat Prot Dosim 1985; 13:223-227.

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